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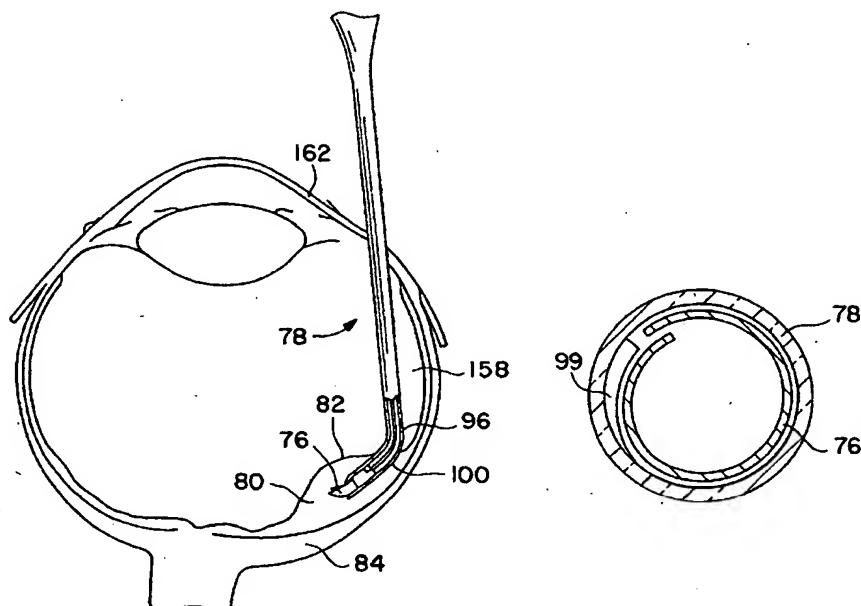
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(54) Title: METHOD FOR PREPARATION AND TRANSPLANTATION OF VOLUTE GRAFTS AND SURGICAL INSTRUMENT THEREFOR

## (57) Abstract

A method of transplanting a graft in the subretinal area of a host eye comprises preparing the graft by harvesting from the donor tissue a population of cells in a manner that maintains the population of cells in the same organization and cellular polarity as is present in normal tissue of that type. The population of cells are of a sheet-like form and are assembled with a relatively thin flexible pliable carrier composed of a non-toxic flexible composition which substantially dissolves at body temperature to form a graft. The graft is sufficiently flexible and pliable to be coiled to form a volute (76) without disturbing the organization and polarity of the cells. The method further comprises coiling the graft to form a volute (76) with the convolutions of the volute (76) free of one

another for subsequent uncoiling of the graft substantially to its original sheet-like form. An incision is made in the host eye for insertion of the volute (76). The incision in the eye is smaller than the incision that would be required for insertion of the graft in its uncoiled sheet-like form. The volute is inserted one end first into the host eye through the incision and transported to a position between the retina and the underlying tissue. The volute (76) uncoils after its insertion to lie in sheet-like form between the retina and the underlying tissue of the host eye. The incision is then closed.



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METHOD FOR PREPARATION AND TRANSPLANTATION OF  
VOLUTE GRAFTS AND SURGICAL INSTRUMENT THEREFOR

BACKGROUND OF THE INVENTION

The present invention relates in general to surgical  
10 instruments and surgical techniques. More particularly, the  
present invention is directed to a surgical tool for  
transplanting sheets of retinal cells, epithelial tissue  
and/or choroidal tissue in a volute configuration through a  
standard-sized incision in the eye, a graft for  
15 transplantation to the subretinal region of the eye, a method  
for preparing such grafts for transplantation and a method for  
reconstructing dystrophic retinas, retinal pigment epithelial  
layers and choroids.

The retina is the sensory epithelial surface that  
20 lines the posterior aspect of the eye, receives the image  
formed by the lens, transduces this image into neural impulses  
and conveys this information to the brain by the optic nerve.  
The retina comprises a number of layers, namely, the ganglion  
cell layer, inner plexiform layer, inner nuclear layer, outer  
25 plexiform layer, outer nuclear layer, photoreceptor inner  
segments and outer segments. The outer nuclear layer  
comprises the cell bodies of the photoreceptor cells with the  
inner and outer segments being extensions of the cell bodies.

The choroid is a vascular membrane containing large  
30 branched pigment cells that lies between the retina and the  
sclerotic coat of the vertebrate eye. Immediately between the  
choroid and the retina is the retinal pigment epithelium which

forms an intimate structural and functional relationship with the photoreceptor cells.

Several forms of blindness are primarily related to the loss of photoreceptor cells caused by defects in the retina, retinal pigment epithelium, choroid or possibly other factors (e.g. intense light, retinal detachment, intraocular bleeding). In several retinal degenerative diseases select populations of cells are lost. Specifically, in macular degeneration and retinitis pigmentosa, the retinal photoreceptors degenerate while other cells in the retina as well as the retina's central connections are maintained. In an effort to recover what was previously thought to be an irreparably injured retina, researchers have suggested various forms of grafts and transplantation techniques, none of which constitute an effective manner for reconstructing a dystrophic retina.

The transplantation of retinal cells to the eye can be traced to a report by Royo et al., Growth 23: 313-336 (1959) in which embryonic retina was transplanted to the anterior chamber of the maternal eye. A variety of cells were reported to survive, including photoreceptors. Subsequently del Cerro was able to repeat and extend these experiments (del Cerro et al., Invest. Ophthalmol. Vis. Sci. 26: 1182-1185, 1985). Soon afterward Turner, et al. Dev. Brain Res. 26:91-104 (1986) showed that neonatal retinal tissue could be transplanted into retinal wounds.

In related studies, Simmons et al., Soc. Neurosci. Abstr. 10: 668 (1984) demonstrated that embryonic retina could be transplanted intracranially, survive, show considerable normal development, be able to innervate central structures, and activate these structures in a light-dependent fashion. Furthermore, these intracranial transplants could elicit light-dependent behavioral responses (pupillary reflex) that

were mediated through the host's nervous system. Klassen et al., Exp. Neurol. 102: 102-108 (1988) and Klassen et al. Proc. Natl. Acad. Sci. USA 84:6958-6960 (1987).

Li and Turner, Exp. Eye Res. 47:911 (1988) have  
5 proposed the transplantation of retinal pigment epithelium (RPE) into the subretinal space as a therapeutic approach in the RCS dystrophic rat to replace defective mutant RPE cells with their healthy wild-type counterparts. According to their approach, RPE was isolated from six- to eight-day old black  
10 eyed rats and grafted into the subretinal space by using a lesion paradigm which penetrates through the sclera and choroid. A 1 ml injection of RPE (40,000 - 60,000 cells) was made at the incision site into the subretinal space by means of a 10 ml syringe to which was attached a 30 gauge needle.  
15 However, this method destroys the cellular polarity and native organization of the donor retinal pigment epithelium which is desirable for transplants.

del Cerro, (del Cerro et al., Invest. Ophthalmol. Vis. Sci. 26: 1182-1185, 1985) reported a method for the  
20 transplantation of tissue strips into the anterior chamber or into the host retina. The strips were prepared by excising the neural retina from the donor eye. The retina was then cut into suitable tissue strips which were then injected into the appropriate location by means of a 30 gauge needle or  
25 micropipette with the width of the strip limited to the inner diameter of the needle (250 micrometers) and the length of the strip being less than 1 millimeter. While del Cerro reports that the intraocular transplantation of retinal strips can survive, he notes that the procedure has some definite  
30 limitations. For instance, his techniques do not allow for the replacement of just the missing cells (e.g. photoreceptors) but always include a mixture of retinal cells. Thus, with such a transplant appropriate reconstruction of the

dystrophic retina that lacks a specific population of cells (e.g., photoreceptors) is not possible.

del Cerro et al., Neurosci. Lett. 92: 21-26, 1988, also reported a procedure for the transplantation of dissociated neuroretinal cells. In this procedure, the donor retina is cut into small pieces, incubated in trypsin for 15 minutes, and triturated into a single cell suspension by aspirating it through a fine pulled pipette. Comparable to the Li and Turner approach discussed above, this procedure destroys the organized native structure of the transplant, including the donor outer nuclear layer; the strict organization of the photoreceptors with the outer segments directed toward the pigment epithelium and the synaptic terminals facing the outer plexiform layer are lost. Furthermore, no means of isolating and purifying any given population of retinal cells (e.g. photoreceptors) from other retinal cells was demonstrated.

It is believed by the present inventor that it is necessary to maintain the photoreceptors in an organized outer nuclear layer structure in order to restore a reasonable degree of vision. This conclusion is based on the well known optical characteristics of photoreceptors (outer segments act as light guides) and clinical evidence showing that folds or similar, even minor disruptions in the retinal geometry can severely degrade visual acuity.

#### SUMMARY OF THE INVENTION

Among the objects of the present invention, therefore, may be noted the provision of a method which conserves relatively large expanses of tissue harvested from a donor eye; the provision of such a method in which a relatively large expanse of harvested tissue is so formed as to enable the harvested tissue to be inserted into a

standard-sized incision in the eye; the provision of such a method in which the polarity and organization of the cells at the time of harvest are maintained in the graft; and the provision of a method for implantation of grafts to the  
5 subretinal area of an eye.

Further among the several objects and features of the present invention may be noted the provision of a graft for use in the reconstruction of a dystrophic retina or rescue of endogenous photoreceptor cells of an individual afflicted  
10 with an inherited or acquired retinal disease which causes a progressive loss of rods and subsequent eventual cone dystrophy, dysfunction and/or loss; the provision of such a graft which facilitates regrowth of photoreceptor axons by maintaining the polar organization of the photoreceptor and  
15 the close proximity of their postsynaptic targets with the adjacent outer plexiform layer upon transplantation.

Further among the several objects and features of the present invention may be noted the provision of a surgical tool for use in the implantation method which forms the graft  
20 for insertion into a standard-sized incision; and the provision of a surgical tool for use in the transplantation method which allows appropriate retinotopic positioning and which protects photoreceptors, retinal pigment epithelial tissue, choroidal tissue and/or Bruch's membrane from damage  
25 prior to and as the surgical device is positioned in the eye.

Generally, the implantation method comprises coiling an implantable material which is of sheet-like form to form a volute. The convolutions of the volute are free of one another for subsequent uncoiling of the implantable material  
30 substantially to its original sheet-like form. An incision is made in the host eye for the insertion of the volute to a position between the retina and the underlying tissue of the host eye. The incision is smaller than the incision that

would be required for insertion of the implantable material in its uncoiled sheet-like form. The volute is inserted one end first into the host eye through the incision to a position between the retina and the underlying tissue. The volute  
5 uncoils after its insertion to lie in sheet-like form between the retina and the underlying tissue of the host eye and the incision is closed.

Generally, the graft for implantation comprises a layer of a non-toxic flexible composition which substantially  
10 dissolves at body temperature and a material to be implanted coiled to form a volute. The volute is insertable one end first through the incision dimensioned in accordance with the cross-sectional area of the volute to a position for implantation, and then uncoiled to lie in sheet-like form at  
15 the site of implantation.

Generally, the implement for the formation of a volute comprises a tubular body open at one end and having a funnel. A carrier enters one end first in the tubular body at the open end thereof and is fed along the body into and  
20 through the funnel. The engagement of the carrier as it is fed through the funnel with an interior surface of the funnel causes the carrier to coil into the volute. The volute exits from a small end of the funnel.

Other objects and features of the invention will be  
25 in part apparent and in part pointed out hereinafter.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a photograph of a cryostat section of normal rat retina as set forth in Example 1;

Fig. 2 is a photograph of a blinded rat retina  
30 following constant illumination as set forth in Example 1;

Fig. 3 is a schematic of a donor retina;

Fig. 4 is a schematic of a flattened retina;



Fig. 5 is a schematic of a flattened retina mounted to a substrate;

Fig. 6 is a schematic of a sectioned retina mounted to a substrate;

5 Fig. 7 is a schematic of a laminate comprising a retina section on a supporting, stabilizing substrate;

Fig. 8 is a schematic top plan view of the laminate of Fig. 7, showing a graft (dashed lines) comprising a photoreceptor cell layer and a supporting, stabilizing  
10 substrate;

Fig. 9 is a schematic of the graft mounted on a plate formed with spacers;

Fig. 10 is a schematic of the graft mounted on a plate infused with molten gelatin with a cover plate;

15 Fig. 11 is a schematic of the top plate being laterally slid off;

Fig. 12 is a schematic of the resulting graft;

Fig. 13 is a schematic of the graft being skived;

Fig. 14 is a schematic of the skived graft being  
20 removed from the plate for transplantation;

Fig. 15 is a perspective view of a volute;

Fig. 16 is a side elevational view of an instrument for coiling and implanting the graft with the coiled graft in the funnel of the instrument;

25 Fig. 17. is a side elevational view of the instrument with a lumen attached to the outside of the instrument;

Fig. 18. is a side elevational view of the instrument with the plunger advancing the volute.;

30 Fig. 19. is a horizontal section through an eye illustrating a pars plana surgical approach with the instrument extending partially across the eye;

Fig. 20. is a horizontal section through an eye illustrating a pars plana surgical approach with the instrument inserted into a bleb; and

Fig. 21. is a horizontal section taken along line 21--21 of Fig. 16 illustrating a ramp within the instrument.

Corresponding reference characters indicate corresponding parts throughout the several views of the drawings.

#### DETAILED DESCRIPTION

As used herein, the term "donor" shall mean the same or different organism relative to the host and the term "donor tissue" shall mean tissue harvested from the same or different organism relative to the host.

Several forms of blindness such as retinitis pigmentosa, retinal detachment, macular degeneration, and light exposure-related blindness, are primarily related to the loss of the photoreceptors in the eye. However, destruction of the photoreceptors does not necessarily lead to the loss of the remaining retina or axons that connect the retina to the brain. Surprisingly, it has been discovered that some degree of vision can be restored by replacing damaged photoreceptors with photoreceptors harvested from a donor and which are maintained in their original organization and cellular polarity. Furthermore, as further described in co-pending Application No 08/033,105 (which is incorporated herein by reference), the transplantation of photoreceptor rods harvested from a donor eye can "rescue" endogenous cone photoreceptors within the retina and thus may restore or preserve visual sensitivity of existing cone photoreceptors. That is, it has been found that transplanted rods exert a trophic effect upon endogenous cone photoreceptors.

Fig. 1 is a photograph of a cryostat section of normal rat retina. Fig. 2 is a photograph of a cryostat section of a rat retina following constant illumination which destroys the photoreceptor (outer nuclear) layer while leaving  
5 other retinal layers and cells largely intact. In these and subsequent figures, the retina or layers thereof, e.g., the ganglion cell layer ("G"), inner plexiform layer ("IPL"), inner nuclear layer ("INL"), outer plexiform layer ("OPL"), outer nuclear layer ("ONL"), inner segments ("IS"), outer  
10 segments ("OS"), and retinal pigment epithelium ("RPE"), are shown, respectively, from top to bottom.

Referring now to Fig. 3, a photoreceptor graft for implantation through an incision smaller than the width of the graft in sheet-like form is prepared in accordance with a  
15 method of the present invention. The graft, however, may comprise other implantable material such as other retinal cells, antiviral and antibiotic agents and/or other pharmacologic agents.

A graft comprising photoreceptor cells is prepared  
20 by removing a donor retina 50 comprising inner retina layers 52 and a photoreceptor layer 54 from a donor eye. The donor retina 50 is flattened (Fig. 4) by making a plurality of cuts through the retina from locations near the center of the retina to the outer edges thereof (see Fig. 8). Cuts can be  
25 made in other directions if necessary.

As shown in Fig. 5, the flattened retina 56 is placed with the photoreceptor side 54 down on a gelatin slab 58 which has been surfaced so as to provide a flat surface 60 that is parallel to the blade of a vibratome apparatus. The  
30 gelatin slab 58 is secured to a conventional vibratome chuck of the vibratome apparatus. Molten four to five per cent gelatin solution is deposited adjacent the flattened retina/gelatin surface interface 61 and is drawn by capillary

action under the flattened retina 56 causing the flattened retina to float upon the gelatin slab 58. Excess molten gelatin is promptly removed and the floating flattened retina 56 is then cooled to approximately 4°C with ice-cold Ringer's solution that surrounds the gelatin block to cause the molten gelatin to gel. The flattened retina 56 is thereby adhered to the gelatin block 58.

As shown in Fig. 6, the inner retina portion 52 is sectioned from the top down at approximately 20 to 50 millimicrons until the photoreceptor layer 54 is reached, thereby isolating the photoreceptor layer from the inner layers of the retina, i.e., the ganglion cell layer, inner plexiform layer, inner nuclear layer, and outer plexiform layer. When the photoreceptor layer 54 is reached, the vibratome stage is advanced and a section from approximately 50 to 300 millimicrons thick is obtained as shown in Fig. 7. The thickness of this section should be sufficient to undercut the photoreceptor and form a section 62 consisting of a layer of photoreceptor cells and a thin gelatin substrate 58 adhered thereto. As shown in Fig. 8, the section 62 is cut vertically along the dashed lines to create a laminate 63.

The laminate 63 is then placed onto a flat plate 64 formed with risers 66 as shown in Fig. 9. The plate 64, with the laminate 63 positioned between the risers 66, is infused with molten fifteen to twenty per cent gelatin solution to surround and cover the photoreceptor layer 54 with the gelatin substrate 58 is surrounded and covered by the molten gelatin. As shown in Fig. 10, a flat cover plate 68 is placed on top of the risers 66 to remove any excess molten gelatin and to establish the precise thickness of the graft. The height of the risers 66 can be adjusted to prepare grafts of different thicknesses.

The resulting container 67 consisting of two plates 64, 68 separated by risers 66 encasing a gelatin slab 69 with the photoreceptor layer 54 embedded therein is cooled to room temperature to cause the molten gelatin to gel and form a carrier sheet 70 encapsulating the photoreceptor layer 54. The outer segment (not shown) of the photoreceptor layer 54 faces toward one face 71 of the carrier sheet 70.

As shown in Fig. 11, after the molten gelatin is allowed to gel, the top cover plate 68 of the laminate is carefully removed by sliding the plate laterally away from the risers 66 so as to prevent any tearing of the gelatin carrier sheet 70 and layer of photoreceptors 54. The risers 66 are likewise removed to expose the carrier sheet 70. To further reduce the risk of tearing the gelatin carrier sheet 70 upon removal of the top cover plate 68 the top cover plate can be wrapped in a TEFLON film (not shown) so that the bottom surface of the cover plate has a smooth layer of film affixed thereto. The top cover plate is removed by unwrapping the film on the upper surface of the cover plate and lifting the plate from the risers 66. The TEFLON film is then carefully peeled from the gelatin carrier sheet 70. Immersion in a dissecting fluid (such as an aqueous solution) can facilitate peeling.

Opposite ends 73 of the carrier sheet 70 are cut vertically to a size appropriate for transplantation. As shown in Fig. 13, opposite sides 72 of the carrier sheet 70 can be skived--cut at obtuse and acute angles relative to the top and bottom surfaces of the gelatin slab--to produce a graft 74 having approximately parallel sides. The skived sides 72 of the graft 74 facilitates the sliding of one side 72 of the graft over the other side. The surface of the graft 74 should have a surface area greater than about 1 square millimeter, preferably greater than 4 square millimeters or as

large as may be practically handled within a surgical instrument for implantation of the graft through an incision in a host eye. Thus constructed, the graft 74 may subtend a considerable extent of the retinal surface.

5           To prepare the graft for insertion into the eye, the graft 74 is removed from the plate 64 (Fig. 14) and formed into a volute 76 (Fig. 15) having overlapping sides 72 and convolutions 77. The convolutions 77 of the volute 76 are free of one another in the sense that the convolutions do not  
10   impede the volute from subsequent uncoiling. Although it is not presently preferred, the sides 72 of the volute 76 do not necessarily need to overlap; any coiled configuration of the graft 74 whereby the diameter of the volute is less than the  
15   distance between the sides 72 of the uncoiled, sheet-like graft and whereby the photoreceptor layer 54 is not damaged may be prepared in accordance with the present invention.

          The thickness of the graft 74 comprising the sectioned flattened retinal tissue 54 and the carrier sheet 70 as discussed above is only approximate and will vary as donor  
20   material varies. In addition, sectioning may be facilitated and vibratome thickness further calibrated from histological measurements of the thickness of the retina, thereby providing further guides to sectioning depth. Appropriate sectioning thicknesses or depth may be further determined by microscopic  
25   examination and observation of the sections.

          The gelatin carrier sheet 70 adds mechanical strength and stability to the easily damaged photoreceptor layer 54. As a result, the flattened retinal tissue 54 is less likely to be damaged and is more easily manipulated  
30   during the transplantation procedure. Gelatin is presently preferred as an encapsulant because of its flexibility, pliability, ability to dissolve at body temperature and apparent lack of toxicity to neural tissue upon dissolution.

However, other compositions such as auger or agarose which also have the desirable characteristics of gelatin may be substituted. Significantly, gelatin has not been found to interfere with tissue growth or post-transplant interaction  
5 between the graft 74 and the underlying retinal pigment epithelium. Gelatin is also presently preferred as an adhesive to laminate the retinal tissue 54 within the encapsulant. However, other compositions, including lectins such as concanavalin A, wheat germ agglutin, or photo reactive  
10 reagents which gel or decompose upon exposure to light and which also have the desirable characteristics of gelatin may be substituted as the adhesive.

Advantageously, the gelatin carrier sheet 70 or other encapsulant may additionally serve as a carrier for any  
15 of a number of trophic factors such as fibroblast growth factor, pharmacologic agents including immunosuppressants such as cyclosporin A, anti-inflammation agents such as dexamethasone, anti-angiogenic factors, anti-glial agents, and anti-mitotic factors. Upon dissolution of the encapsulant,  
20 the factor or agent becomes available to impart the desired effect upon the surrounding tissue. The dosage can be determined by established experimental techniques. The encapsulant may contain biodegradable polymers to act as slow release agents for pharmacologic substances that may be  
25 included in the encapsulant.

As an alternative to mechanical, e.g., microtome, sectioning, the donor retina 50 may be chemically sectioned. Specifically, it is known that neurotoxic agents such as kainic acid or anoxia are toxic to cells in all retinal layers  
30 52 except to photoreceptors and Müller cells. Therefore if the donor retina 50 is treated with an appropriate neurotoxic agent the photoreceptor layer 54 can be isolated. This technique has the advantage of maintaining the retinal Müller

cells (which are relatively insensitive to kainic acid and anoxia) with the photoreceptor cells 54. Since it is known that Müller cells help maintain photoreceptor cells 54 (both biochemically and structurally) the isolation of Müller cells  
5 along with the photoreceptor cells could be advantageous.

If desired, the graft 74 may contain retinal pigment epithelial cells. Because the RPE is tenuously adherent to the retina, mechanical detachment of the retina from a donor eye ordinarily will cause the RPE to separate from the retina  
10 and remain attached to the choroid. However, through the use of enzymatic techniques such as those described in Mayerson et al., Invest. Ophthalmol. Vis. Sci. 25: 1599-1609, 1985, the retina can be separated from the donor eye with the RPE attached. Alternatively, implants comprising a monolayer of  
15 RPE cells can be prepared by harvesting RPE cells from donor tissue and apposing the harvested RPE cells as an intact monolayer to a non-toxic, flexible composition, or by seeding such a composition with a monolayer of dissociated RPE cells and allowing them to grow into a confluent layer. The  
20 flexible composition serves as a stabilizing support for the RPE cells during encapsulation and transplantation.

Grafts comprising the choroid, Bruch's membrane or a synthetic Bruch's membrane (e.g., collagen sheet on the order of 1-5 microns) may also be prepared. The choroid is stripped  
25 off of the scleral lining of the eye (with or without the RPE attached) and flattened by making radial cuts. The donor choroid may be encapsulated as previously described for the photoreceptor cells and/or combined with a photoreceptor layer 54 which has been prepared as described above to form a  
30 laminate comprising a photoreceptor layer and a choroidal layer encapsulated within a gelatin substrate and superstrate.

Referring to Figs. 16-18, there is shown a surgical instrument 78 for creating a volute 76 and implanting the



volute at the transplantation site of the host eye. The surgical instrument 78 and method of this invention are particularly adapted for the isolation and transplantation of an intact sheet of cells from a donor retina to a recipient  
5 retina through an incision which is smaller than the incision that would be required for insertion of the graft 74 in its uncoiled sheet-like form and the instrument 78 and method are further characterized by the maintenance of cell organization of the transplanted tissue layer.

10 An embodiment of an instrument 78 for implanting an intact cellular structure 74 between the retina and supporting tissues in an eye is indicated generally in Figure 16. The instrument 78 may be made from acrylic, glass or some other suitable material that is sterilizable. The instrument 78  
15 comprises a tubular body 90 open at one end 92 for receiving the generally planar cellular structure 74, a tapered passage or funnel 94 for coiling the planar structure 74 into a volute 76, and a tubular tip 96 for insertion into the host eye. As shown and described herein, the instrument 78 is approximately  
20 10 to 15 centimeters long, which is an appropriate length for making implants in rodents and lower primates. The narrow tubular tip 96 which is inserted into the incision of the eye--the eye port--must be sufficiently long to extend into the eye to reach in between the retina and the supporting  
25 sub-retinal tissue. Different lengths may be used for the narrow tubular tip 96 of the instrument 78 depending upon the procedure being employed and upon the recipient.

As shown in Fig. 21, the instrument 78 may include a ramp 99 on the inside surface of the instrument at the  
30 transition from the tubular body 90 to the funnel 94. The ramp directs one side 72 underneath the other side of the graft 74 to form volute 76. In this embodiment of the instrument 78, the side edges 72 of the carrier sheet 70 can

be cut vertically, instead of skived to form graft 74. The ramp 99 prevents buckling of the graft 74 by not permitting the side edges to contact each other and can act to align the volute in a specific orientation (e.g., one edge of the volute can be maintained in a particular orientation).

As shown and described herein, the inner diameter of the instrument 78 is approximately 5 millimeters at its open end 92 and 800 microns at its tubular tip 96. The inner diameter of the tubular tip 96 must be sized to allow an intact coiled cellular structure--i.e., a volute 76--to pass therethrough for implantation without causing the convolutions 77 of the volute to create shear stress on one another and thus possibly cause damage to the photoreceptor layer 54 embedded therewithin. Thus, different tubular diameters may be used depending upon the recipient and the size of the graft 74. Furthermore, the transition in the funnel 94 from the diameter of the open end 92 to the diameter at the narrow tubular tip 96 cannot be too abrupt as to cause graft 74 to buckle. Accordingly, the slope of funnel 94 is gradual to allow for controlled coiling of the graft 74.

As shown in Figure 18, the edge 98 of the narrow tubular tip 96 of the instrument 78 can be beveled to facilitate both the insertion of the instrument into the eye and the advancement of the tubular tip into the subretinal tissue of the eye with a minimum of trauma. Further, as shown in Fig. 20, the beveled edge 98 of the tubular tip 96 facilitates the gradual uncoiling of the graft 74 as one end of the graft is being ejected from the tubular tip. The edge 98 of the tubular tip 96 is preferably beveled at about 45°, from the top to the bottom. The narrow tubular tip 96 of the instrument 78 is preferably curved along its longitudinal axis from the edge 98 of the tubular tip to the small end of the funnel 94, as generally indicated at 100. The curvature 100

of the tubular tip 96 facilitates the manipulation of the instrument 78 within the eye; particularly the manipulation of the instrument to a position between the retina 82 and the supporting tissue 84 on the curved walls of the eye. The  
5 radius of the curvature 100 of the tubular tip 96 will depend upon the procedure and the radius of curvature of the host eye.

The instrument 78 further comprises plunger means 35 to assist the graft 74 through the narrow tubular tip 96. As  
10 shown in Figure 18, the plunger means 85 is preferably a thin tubular plunger 86 received in the open end 92 of the tubular body 90 so that relative advancement of the plunger through the funnel 94 and into the tubular tip 96 with respect to the tubular body urges the coiled cellular structure 76 through  
15 the funnel of the tubular body and through the tubular tip of the instrument 78. To reduce damage to the fragile cellular structure 76 caused by direct contact between the plunger 86 and the cellular structure, the coiled cellular structure is protected from direct contact with the plunger 86 by a spacer  
20 made from gelfoam 102 or other soft compressible material which is inserted into the open end 92 of the tubular body 90 prior to the insertion of the plunger. The gelfoam 102 is guided to lay on top of the coiled cellular structure 76 and thereby protects the coil from direct contact with the  
25 mechanical plunger 86. Gelfoam is satisfactory because it is semi-solid and non-toxic. The plunger 86 projects a sufficient distance from the open end 92 of the tubular body 90 so that the projecting end 88 of the plunger can be manipulated even when the tubular tip 96 of the instrument 78  
30 is in the eye. The preferred method of operating the instrument 78 is that once the tubular tip 96 with the coiled cellular structure 76 therein is properly located within the subretinal area 80 of the eye, the plunger 86 is manipulated

to eject the coiled cellular structure 76 from the tubular tip 96 of the instrument. While the plunger 86 provides the greatest control over the ejection of the volute 76 into the eye, some caution must be exercised while operating the  
5 plunger because of the increased likelihood of damage to the volute 76.

Alternatively, the plunger means 85 may comprise means for applying fluid pressure (not shown) on the contents of the tubular body 90. In this case, the open end 92 of the  
10 tubular body is connected to a line connected to a source of fluid under pressure. Fluid can be selectively supplied via the line to the open end 92 of the instrument 78 to displace its contents. The fluid may be viscous, for example a 2% carboxymethylcellulose, or non-viscous. Particularly in the  
15 later case, it may be desirable to have gelfoam or some other relatively soft spacer material in the tube to act as a mechanical plunger and to separate the fluid from the cell structure being implanted. As previously discussed, gelatin is satisfactory to protect the volute because it is semi-solid  
20 and will dissolve harmlessly if it is ejected from the instrument. While the use of fluid pressure as the plunger means 85 significantly decreases the likelihood of damage to the volute 76, it also results in a significant reduction in the degree of control over the ejection of the volute 76 from  
25 the instrument 78.

As shown and described in parent application Serial No. 07/566,996 (which is incorporated herein by reference), numerous features can be included with the instrument to facilitate a particular surgery. As shown in Fig. 17, the  
30 instrument may include a lumen 108 extending generally parallel with the instrument 78. As used herein, lumen 108 refers to any tube-like vessel, whether separately provided or formed as a passageway on the outside of the instrument 78.

The lumen 108 has a distal end 110 generally adjacent the tubular tip 96 of the instrument 78, and preferably slightly advanced relative to the tubular tip. The proximal end 112 of the lumen 108 is remote from the distal end 110 and may be provided with a connector for connection with a source of fluid under pressure. Thus, the lumen 108 can eject a stream of fluid from its distal end 110 to create a fluid space ahead of the instrument 78. The tubular tip 96 of the instrument 78 follows generally in the path opened by the fluid thus minimizing direct contact of the instrument and the eye tissue. The distal end 110 of the lumen 108 may be beveled to facilitate the advancement of the instrument 78, particularly at times when fluid is not being ejected from the lumen. The end 110 is preferably beveled at about 45°. The fluid ejected from the lumen 108 may be a saline solution, or some other fluid that will not harm the delicate eye tissues. Various substances, such as anti-oxidants, anti-inflammatories, anti-mitotic agents and local anesthetics can be provided in the fluid for treatment of the eye or implanted tissue.

Depending on the type of surgery, the instrument may also include a fiber optic filament (not shown) extending generally parallel with lumen 108, and positioned between the lumen and the tubular body 90. The fiber optic filament facilitates the manipulation of the instrument 78 and the proper placement of the graft 74 in two ways: a light source can be provided at the proximal end of the fiber optic filament so that the filament provides light at the tubular tip 96 of the instrument 78, to facilitate the visual observation procedure through the pupil; alternatively, a lens could be provided at the proximal end of the fiber optic filament so that the filament can be used for direct observation at the tubular tip of the instrument. Additionally, the fiber optic filament could allow for

laser-light cautery to control subretinal bleeding.

The instrument 78 can further include a second lumen (not shown) extending generally parallel with first lumen 108, and positioned between the lumen 108 and the tubular body 90.

- 5 The second lumen allows for the aspiration of material from the tubular tip 96 of the instrument 78. The proximal end of the lumen can be connected to a source of suction so as to remove excess fluid and debris.

- 10 The instrument 78 can further include a pair of lead wires (not shown) terminating in an electrode at their distal ends. The electrode allows for cauterization of blood vessels. The proximal ends of the leads can be connected to a source of electrical power to seal broken blood vessels. It is possible to incorporate the leads onto the wall of the  
15 tubular body 90 of the instrument 78.

Of course, two or more of the features described with respect to the alternate embodiments could be combined, as necessitated by the particular circumstances.

- 20 The method of transplanting a volute 76 into the subretinal area of an eye comprises assembling a transplantable material such as retinal pigment epithelial tissue, choroidal tissue, Bruch's membrane and/or retinal cells 54 into a graft 74 as previously described. It will be understood that the transplantable material may be formed into  
25 a graft without the gelatin carrier sheet and still be within the scope of the present invention. Preferably, however, the graft is assembled with a carrier sheet 70. The transplantation method provides for the graft 74 to be placed in the instrument at the open end 92 of the tubular body 90  
30 with the graft 74 engaging the interior wall of the tubular body. The graft 74 is placed, one end 73 first, in the open end 92 of the tubular body 90 so that the carrier 70 will be coiled with the outer segments of the photoreceptor layer 54

facing toward the outside of the convolutions 77 of the resultant volute 76 and so that the volute will uncoil in said subretinal area 80 with the outer segment of the photoreceptor layer facing toward the pigment epithelial layer 84 of the host eye. The tubular tip 96 of the instrument 78 is capped 118 and the tubular body 90 is filled with viscoelastic fluid 120 which facilitates the graft's progression into the tapered passage or funnel 94. The graft 74 slidably proceeds into the funnel 94 engaging the progressively narrowing tapered surface causing the graft to progressively coil. As the interior walls of the funnel 94 narrow sufficiently to cause the sides 72 of the carrier sheet 70 to make contact, one side 72 of the sheet 70 slides underneath the other side of the carrier sheet due, in part, to the carrier's skived sides. The skived sides 72 prevent any buckling of the carrier sheet 70 as the side edges make contact. In the alternative embodiment shown in Fig. 21, as the interior walls of the instrument 78 narrow sufficiently to cause the sides 72 of the graft 74 to be in proximity to each other, ramp 99 directs one side underneath the other side to begin the coiling of the volute 76. At some point in the funnel 94 the convolutions 77 of the coil 76 are sufficiently constricted so that the viscoelastic fluid 120 can no longer force the coil through the funnel. A gelfoam spacer 102 is placed on top of the coil 76, a bulb 104 is placed on the open end 92 of the instrument to create a vacuum so that the fluid 120 and the volute 76 remain in the instrument 78, and the cap 118 is removed from the tubular tip 96 of the instrument 78. A syringe 106 can be inserted through the bulb 104 to inject more fluid 120 as required. The plunger 86 is inserted through the bulb 104 into the open end 92 of the tubular body 90 and manipulated to be in contact with the gelfoam spacer 102. The plunger 86 is carefully advanced to force the graft 74 through the funnel 94 to

further coil the graft into a volute 76 and into and through the curved path 100 of the tubular tip 96.

The host eye is prepared so as to reduce bleeding and surgical trauma. A scleral pars plana surgical approach to the subretinal space is preferred (Fig. 20), but other approaches, such as transcorneal and trans-scleral, may be used. A small incision (about 0.75 mm - 2.0 mm) is made in the pars plana large enough to insert surgical instrument 78. Following vitrectomy, the eye can be cooled by infusion of cooled balanced salt solution through a second pars plana port into the vitreal cavity of the eye 112, to avoid dissolution of the carrier sheet 70 of the volute 76 during the surgical procedure. A portion of the retina 82 at the site of implantation is raised away from the pigment epithelial cell lining 84 by making an incision 122 in the retina and infusing balanced salt solution in the subretinal area to form a bleb 80 at the implantation site of the retina 82. If the instrument 78 includes a lumen 108, the retina 82 may be detached by the gentle force of a perfusate such as a saline-like fluid, carboxymethylcellulose, or 1-2% hyaluronic acid ejected from the lumen to create a bleb 80. Advantageously, the fluid may additionally contain anti-oxidants, anti-inflammation agents, anesthetics or agents that slow the metabolic demand of the host retina 82.

The instrument 78 with the volute 76 at its tubular tip 96 is inserted through the pars plana port, through the vitreal cavity and into the subretinal space. As illustrated in Fig. 20, the instrument 78 is then manipulated so that the edge 98 of the tubular tip 96 is in line with the incision 122 of the bleb 80. The entire tip 96 of the instrument 78 is inserted in the bleb 80 and the volute 76 is ejected by carefully advancing the plunger. The volute 76 is ejected from the beveled edge 98 of the tubular tip 96 and uncoils



under its inherent uncoiling memory as it is ejected from the bevelled edge so that the outer segments of photoreceptor layer 54 is facing the pigment epithelial layer 84. If the volute 76 does not uncoil entirely, micro picks can be used to  
5 completely uncoil the graft 74.

The bleb 80 is then deflated by evacuation of fluid within the bleb or by tempanade so that the graft 74 is held in a sandwich-like arrangement at the desired position by the retina 82 and pigment epithelial cell lining 84. The incision  
10 122 of the bleb 80 may be closed cauterly. The gelatin carrier sheet 70 dissolves when it reaches normal body temperature. The edges of the scleral incision are abutted after removal of the forceps and sutured using standard opthamalogic procedures.

15 As shown and described in parent application Serial No. 07/566,996, a trans-choroidal, scleral and corneal surgical approach may be used as an alternative to the pars plana approach described above. Except for the point of entry, the surgical technique is essentially the same as  
20 outlined above. In view of the above, it will be seen that the several objects of the invention are achieved and other advantages attained.

As various changes could be made in the above surgical instruments, compositions of matter and methods  
25 without departing from the scope of the invention, it is intended that all matter contained in the above description or shown in the accompanying drawings shall be interpreted as illustrative and not in a limiting sense.

CLAIMS:

## WHAT IS CLAIMED IS:

1. A method of implanting in the subretinal area of a host eye a volute, the method comprising;  
making an incision in the host eye for the insertion of a volute, one end first, in the host eye to a position  
5 between the retina and the underlying tissue of the host eye, the volute comprising an implantable material having a sheet-like configuration which has been coiled to form a volute with convolutions of the volute free of one another for subsequent uncoiling of the implantable material substantially  
10 to its original sheet-like form,  
inserting the volute one end first into the host eye through the incision to said position between the retina and the underlying tissue,  
the volute uncoiling after its insertion to lie in  
15 sheet-like form between the retina and the underlying tissue of the host eye, and  
closing the incision.
2. The method of claim 1 wherein the implantable material comprises a population of cells which is in the same organization and cellular polarity as is present in normal tissue of that type, said population of cells being of  
5 sheet-like form.
3. The method of claim 2 wherein the population of cells is selected from retinal cells, epithelial tissue, choroidal tissue and Bruch's membrane.

4. A method of transplanting in the subretinal area of a host eye a graft comprising cells from donor tissue taken from a donor eye, the method comprising;

harvesting from the donor tissue a population of  
5 cells in a manner that maintains the population of cells in the same organization and cellular polarity as is present in normal tissue of that type, said population of cells being of sheet-like form,

assembling said population of cells with a  
10 relatively thin flexible pliable carrier composed of a non-toxic flexible composition which substantially dissolves at body temperature to form a graft, the graft being of sheet-like form and sufficiently flexible and pliable to be coiled to form a volute without disturbing said organization  
15 and polarity,

coiling the graft to form a volute with the convolutions of the volute free of one another for subsequent uncoiling of the volute, to its original sheet-like form,

making an incision in the host eye for the insertion  
20 of the volute, one end first, in the host eye, said incision being smaller than the incision that would be required for insertion of the graft in its uncoiled sheet-like form,

inserting the volute one end first into the host eye through the incision to a position between the retina and the  
25 underlying tissue,

the volute uncoiling after its insertion to lie in sheet-like form between the retina and the underlying tissue of the host eye, and

closing the incision.

5. The method of claim 4 wherein the population of cells are selected from the retinal cells, epithelial tissue, choroidal tissue and Bruch's membrane.

6. The method of claim 4 wherein an apical surface of the cells face toward one face of the carrier and the carrier is coiled with said face toward the inside of the convolutions of the resultant volute.

7. The method of claim 4 wherein the cells are embedded in the carrier.

8. The method of claim 7 wherein an apical surface of the cells face toward one face of the carrier and the carrier is coiled with said face toward the inside of the convolutions of the resultant volute, and the volute is  
5 uncoiled in said subretinal area with the apical surface of the cells facing the retina.

9. The method of claim 4 wherein the carrier is of generally rectangular shape having opposite ends and opposite sides and wherein the carrier is coiled to form it into the volute by feeding it endwise one end first through a tapered  
5 passage in the direction from the large end to the small end of the tapered passage, engagement of the carrier with the tapering surface defined by the tapered passage causing the carrier to curl into the volute.

10. The method of claim 9 wherein the volute exiting from the small end of said tapered passage is guided into the host eye to a position between the retina of the host eye and the underlying tissue, where it uncoils under its  
5 inherent uncoiling memory.

11. The method of claim 9 wherein the opposite sides of the carrier are skived for facilitating slippage of one side of the carrier over the other as the carrier is fed endwise through the tapered passage.

12. A method of preparing a graft for implantation in the subretinal area of a host eye, the method comprising coiling an implantable material having a sheet-like configuration to form a volute by placing the implantable  
5 material one end first in a tubular body at an open end thereof and feeding the implantable material along the body into and through a funnel, whereby engagement of the implantable material as it is fed through the funnel with an interior surface of the funnel coils the implantable material  
10 into the volute, the volute exiting from a small end of the funnel.

13. A volute formed in accordance with the process of claim 12.

14. A graft for implantation to the subretinal area of an eye, the graft comprising a volute coiled from a sheet-like non-toxic flexible composition which substantially dissolves at body temperature, the volute having a diameter  
5 less than about two millimeters.

15. The graft of claim 14 wherein the volute has an inherent memory and uncoils under said memory to lie in sheet-like form at the site of implantation.

16. A graft for transplantation in the subretinal area of a host eye comprising a volute coiled from a sheet comprising a layer of a non-toxic flexible composition which substantially dissolves at body temperature and a population  
5 of cells selected from the retinal cells, epithelial tissue, choroidal tissue and Bruch's membrane harvested from donor tissue carried by said sheet, the volute being insertable one end first through an incision in the host eye dimensioned in accordance with the cross-sectional area of the volute to a  
10 position between the retina and the underlying tissue of the host eye, and then uncoiled to lie in sheet-like form between the retina and the underlying tissue of the host eye.

17. A graft as set forth in claim 16 wherein said population of cells is embedded in said sheet.

18. A graft as set forth in claim 16 in combination with an implement for inserting said graft formed in a volute through an incision in the host eye dimensioned in accordance with the cross-sectional area of the volute to a position  
5 between the retina and the underlying tissue of the host eye.

19. An implement for the formation of a volute comprising a tubular body open at one end and having a funnel at its other end whereby a graft is entered one end first in the tubular body at the open end thereof and fed along the  
5 body into and through the funnel, engagement of the graft as it is fed through the funnel with an interior surface of the funnel causing the graft to coil into the volute, the volute exiting from a small end of the funnel.

20. The implement of claim 19 wherein the implement for the formation of a volute is insertable in the subretinal area of an eye for implantation of the graft.

21. The implement of claim 20 wherein the implement further comprises a tubular tip extending from the small end of the funnel, and wherein the tip is insertable through a standard size incision into the eye, the volute, formed in the  
5 funnel, passing through the tip into the subretinal area of the host eye.

22. The implement of claim 21 wherein the tubular tip comprises a bevelled edge.

23. The implement of claim 21 wherein the implement further comprises a ramp to facilitate the coiling of the graft into the volute.

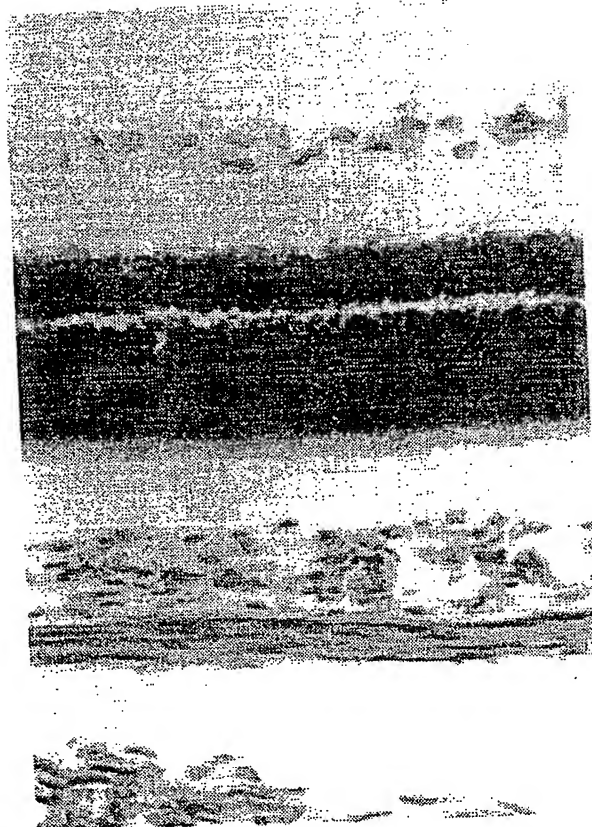
24. The implement of claim 21 wherein the instrument further comprises plunger means for ejecting the volute from the tubular tip of the implement.

25. The implement of claim 24 wherein the plunger means comprises a plunger for ejecting the volute from the tubular tip of the implement.

26. The implement of claim 24 wherein the plunger means comprises fluid pressure means for ejecting the volute from the tubular tip of the implement.

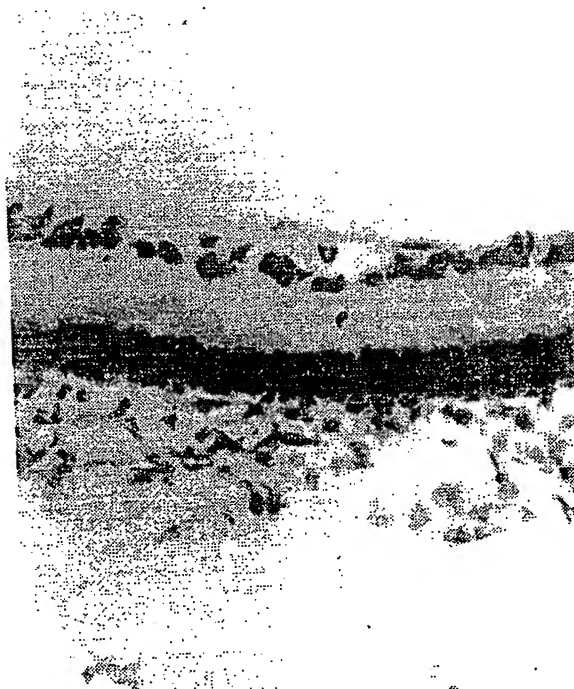
27. The implement of claim 24 wherein the tubular tip is curved along its longitudinal axis.

FIG.1



G  
IPL  
INL  
—OPL  
ONL  
—IS  
OS

FIG.2



G  
IPL  
INL



FIG.3

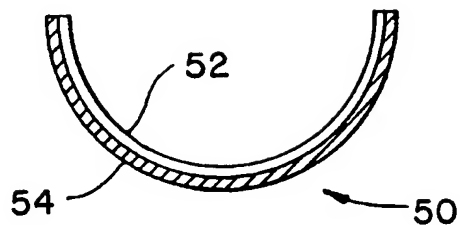


FIG.4

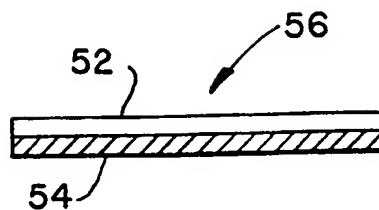


FIG.5

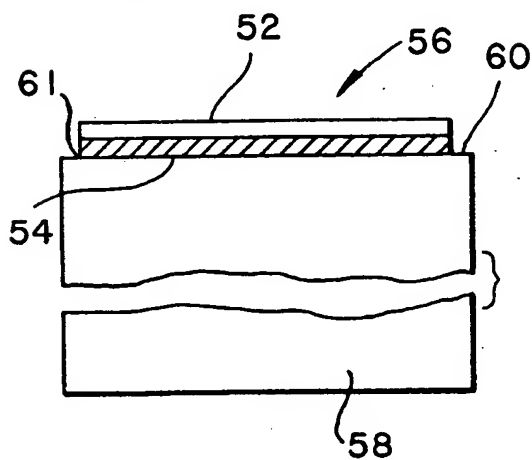


FIG.6

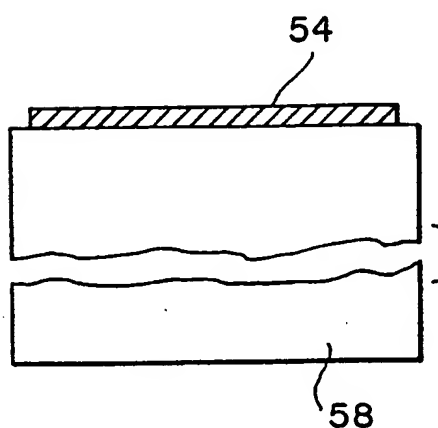


FIG.7

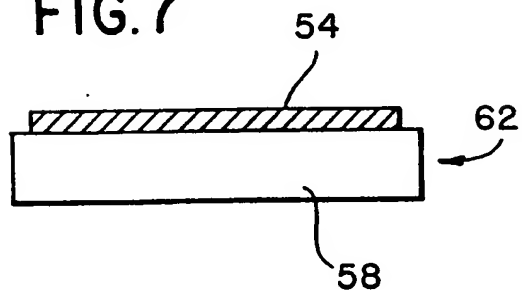
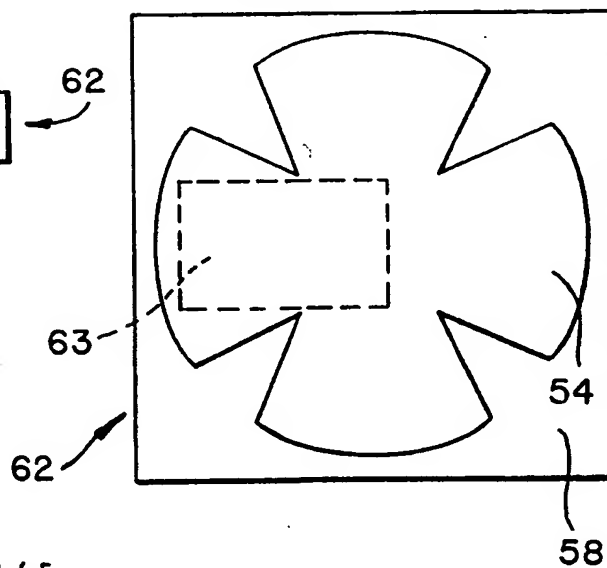
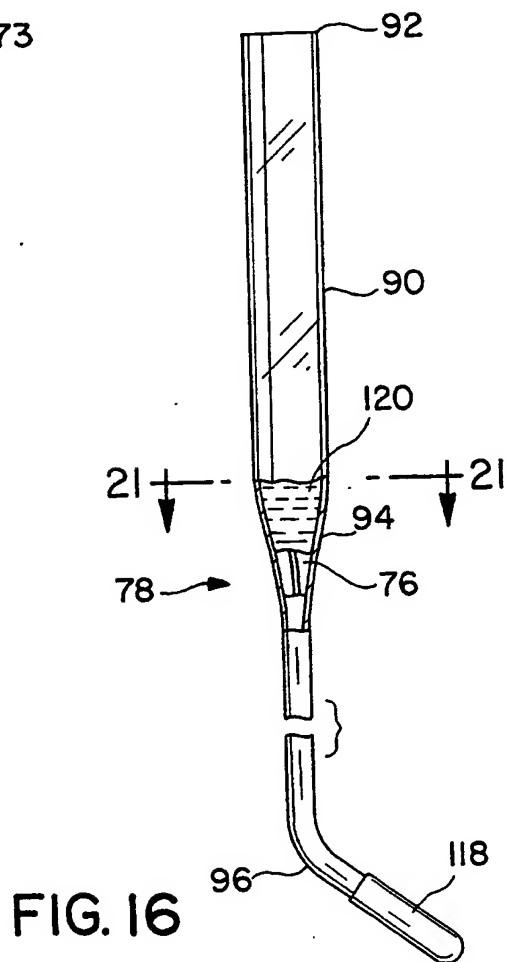
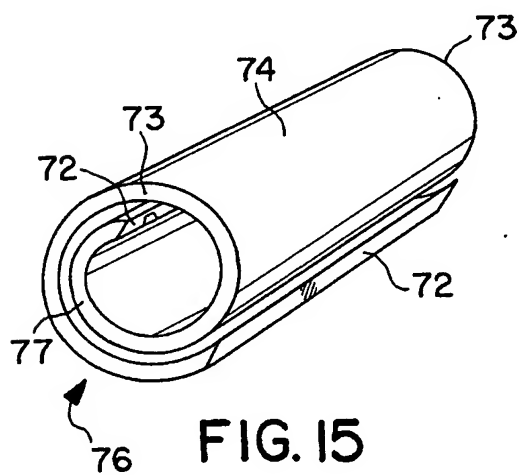
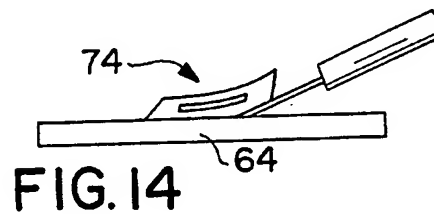
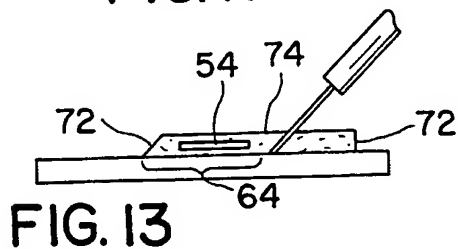
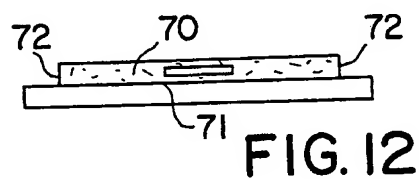
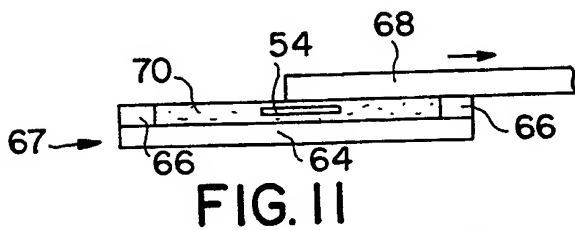
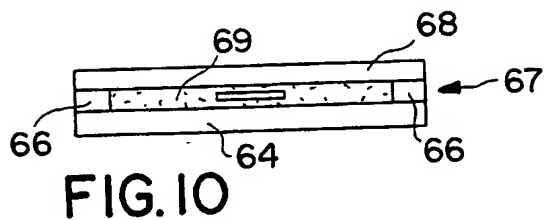
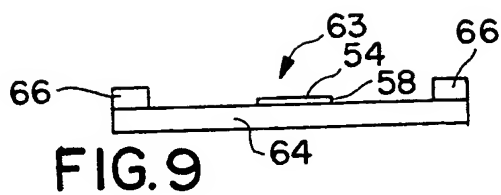
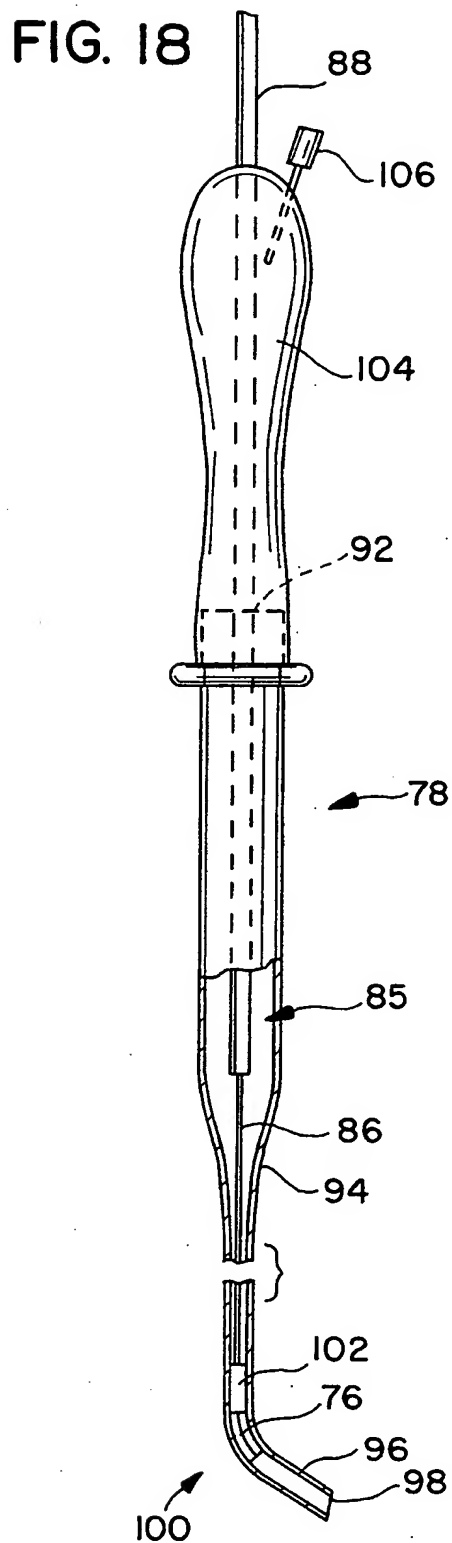
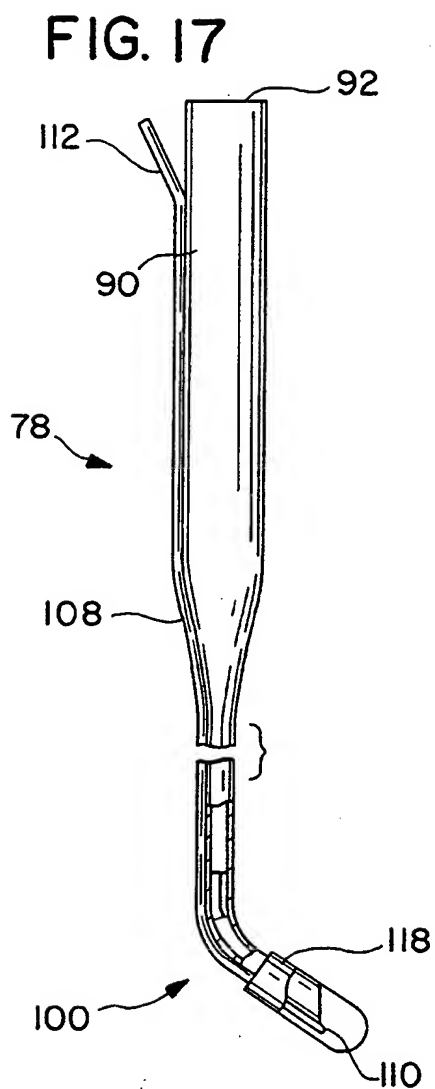
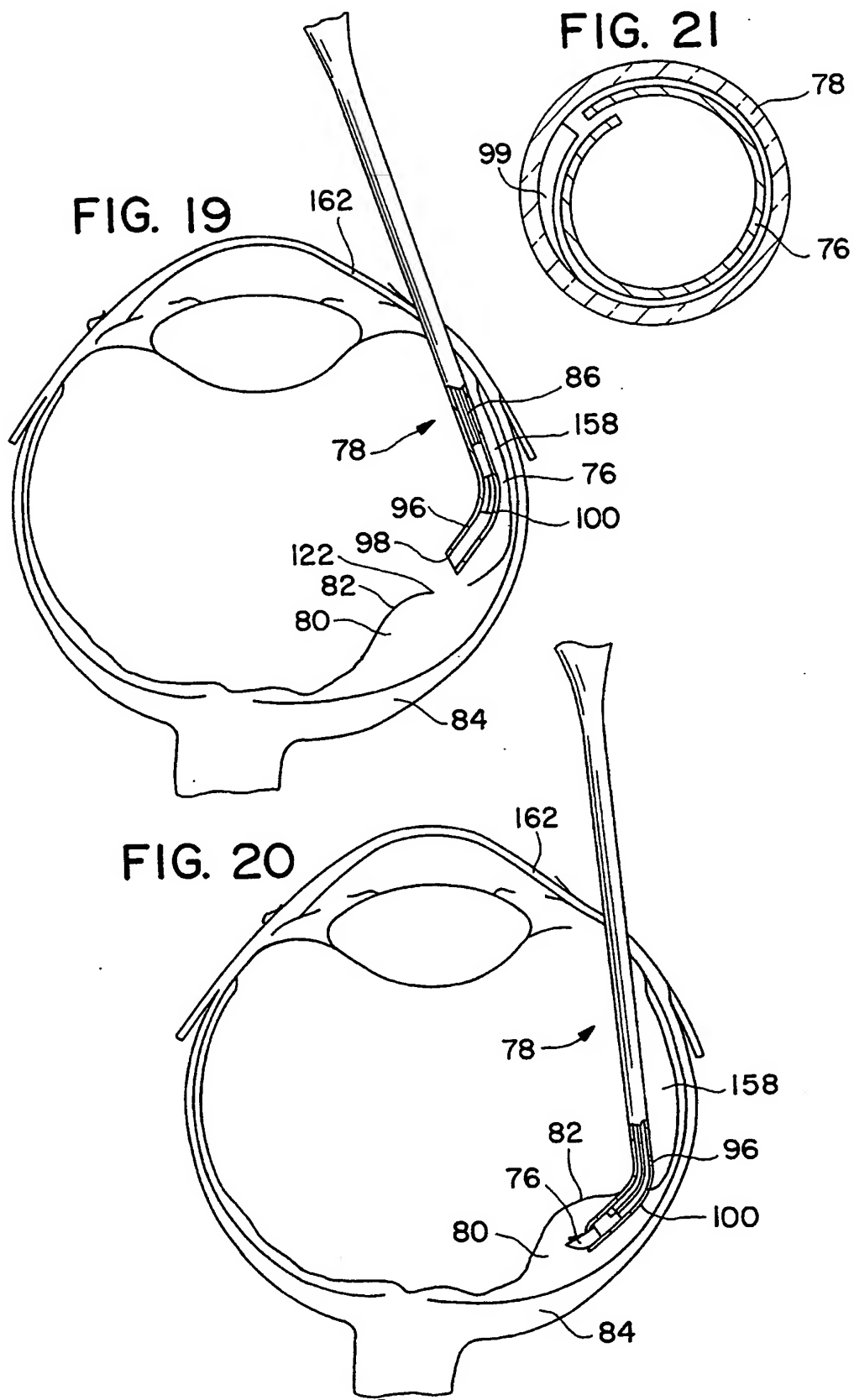


FIG.8









## INTERNATIONAL SEARCH REPORT

PCT/US 93/08616

International Application No

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61F9/00; A61F2/14		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. 5	A61F ; A61B	
Documentation Searched other than Minimum Documentation to the extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	EP,A,0 340 698 (ARCOFIL) 8 November 1989	19
Y	see abstract	12-18, 20-27
	see column 5, line 22 - column 6, line 7 ---	
Y	WO,A,9 102 499 (CENTRAL INSTITUTE FOR THE DEAF) 7 March 1991 see page 18, line 30 - page 23, line 35; figures 3-20 ---	12-18, 20-27
X	DE,A,4 004 921 (K. MEES) 22 August 1991	19
A	see column 3, line 43 - column 4, line 11; figures 1,2 ---	12,13, 21,22
	---	
	-/--	
<sup>10</sup> Special categories of cited documents : <sup>11</sup> "A" document defining the general state of the art which is not considered to be of particular relevance <sup>12</sup> "E" earlier document but published on or after the international filing date <sup>13</sup> "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) <sup>14</sup> "O" document referring to an oral disclosure, use, exhibition or other means <sup>15</sup> "P" document published prior to the international filing date but later than the priority date claimed <sup>16</sup> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention <sup>17</sup> "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step <sup>18</sup> "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. <sup>19</sup> "&" document member of the same patent family		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
26 OCTOBER 1993	11. 11. 93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	WOLF C.	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED) FROM THE SECOND SHEET		Relevant to Claim No.
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	
P,A	EP,A,0 535 506 (WISAP) 7 April 1993 see abstract ---	12, 14, 16, 19
A	WO,A,9 208 406 (THE UNIVERSITY OF ROCHESTER) 29 May 1992 -----	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 93/ 08616

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-11  
because they relate to subject matter not required to be searched by this Authority, namely:  
Method for treatment of the human body by surgery.  
Please see Rule 39.1(iv) PCT.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9308616  
SA 79554

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on  
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26/10/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0340698	08-11-89	CH-A- 675828	15-11-90
		AU-A- 3444289	29-11-89
		WO-A- 8910729	16-11-89
		JP-T- 2504002	22-11-90
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WO-A-9102499	07-03-91	AU-A- 6271590	03-04-91
		EP-A- 0486589	27-05-92
		JP-T- 5501969	15-04-93
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DE-A-4004921	22-08-91	None	
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EP-A-0535506	07-04-93	DE-A- 4132855	08-04-93
		AU-A- 2616792	08-04-93
		CA-A- 2079516	03-04-93
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WO-A-9208406	29-05-92	AU-A- 9062891	11-06-92
		CA-A- 2096006	15-05-92
		EP-A- 0557445	01-09-93
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EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82



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